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A review on the sulfur ylide-mediated Corey–Chaykovsky reaction: a powerful approach to natural product synthesis

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The Corey–Chaykovsky reaction is an efficient transformation in organic syntheses, which enables the construction of 3-membered cores *via* a sulfur ylide-mediated process. The reaction enables a simple yet versatile strategy to access cyclopropanes, epoxides and aziridines. The resulting cyclic frameworks are significantly valuable for the synthesis of several structurally complex compounds, including numerous natural products and their analogues. This review underscores the importance and utility of the Corey–Chaykovsky reaction towards the total synthesis of several classes of natural products reported since 2020.

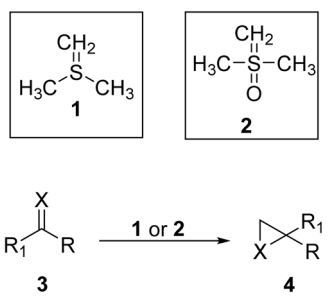
1 Introduction

C–C bond-forming reactions are ubiquitously employed in organic transformations to carry out chain elongation and functionalization.[1–3] In organic synthesis, the Corey–Chaykovsky reaction (CCR), introduced by Corey and Chaykovsky in 1960, is a significant carbon–carbon bond-forming reaction that deals with the efficacious synthesis of aziridine, cyclopropane and epoxide through the reaction of respective functionalized olefinic compounds with dimethylsulfonium methylide **1** or Corey's ylide (dimethylsulfoxonium methylide) **2** (Scheme 1). The functionalized olefinic compound may include imine, carbonyl, enones or thiocarbonyl.[4–7]

In the classic Corey–Chaykovsky reaction, the deprotonation of sulfoxonium and sulfonium halides generates ylides in the presence of a strong base, and the resulting ylides react with ketones/aldehydes and enones to yield oxirane and cyclopropylketones, respectively. The typically used bases are NaH, *t*BuOK and BuLi, with THF, dioxane and DMF employed as solvents.[1,8–14]

Johnson and colleagues first documented the mechanism for the CCR using a carbonyl group and sulfonium ylide, which has received acceptance from the scientific community. Sulfonium ylide **5** nucleophilically attacks the electrophilic center of **6** to form a zwitterionic intermediate, **A**. The intermediate **A** yields a 3-membered ring **8**, facilitated by an intramolecular S_N2 reaction, where X is the nucleophile and sulfide is the leaving group (Fig. 1). For all other sulfide derivatives, the same mechanism may be employed. The sulfonium ylide, being more reactive, reacts with deactivated ketones, whereas the oxosulfonium ylide remains inert. Upon reaction *via* α–β unsaturated ketones, oxosulfonium selectively adds to the olefinic bond, whereas sulfonium ylide may generate oxirane or cyclopropane depending on the substituent (Fig. 1).[15–17]

Since the discovery of the Corey–Chaykovsky reaction, various research groups have employed several methodological modifications to carry out the facile synthesis of targeted



Scheme 1 General representation of the Corey–Chaykovsky reaction.

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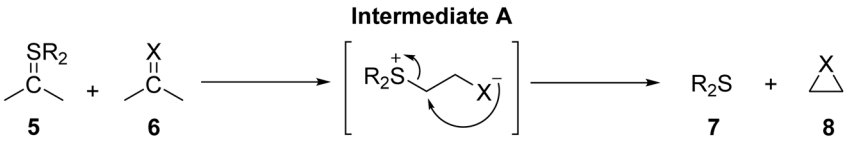


Fig. 1 General mechanism for the Corey–Chaykovsky reaction.

molecules to address challenges such as the stereo-control, structural complexity and chemoselectivity of the reactions with α, β-unsaturated ketones. The recent methodological development of the Corey–Chaykovsky reaction includes the following: the fluoromethyl sulfonium reagent for the synthesis of fluorocyclopropane derivatives,[18] Amberlyst-A26 (ref. 19) as the base for direct cyclopropanation, and a metal-free approach involving ILs[20] as the catalyst and solvent. These innovations provide a valuable alternative to classical methods, enhancing the scope and versatility of the reaction.

Several heterocyclic scaffolds are of significant interest in medicinal and synthetic chemistry owing to their vast biological activities.[22–24] The CCR proceeds *via* the introduction of sulfur ylide to electrophiles (enones, carbonyls, imines), serving as an essential tool in the formation of three-membered rings (cyclopropane, epoxide and aziridine) and a variety of different compounds.[25,26] Owing to the easy handling and affordability of the reactants, the CCR is a robust technique for cyclopropane synthesis. It has gained prominence over the past decade due to the significant advancement of donor–acceptor cyclopropane chemistry.[27–30] Cyclopropanes are ubiquitous moieties with versatile effects in agrochemicals and pharmaceuticals.[31] Several biologically active natural products have also been found to include a cyclopropane ring in their structural frameworks.[32–35]

The Johnson–Corey–Chaykovsky epoxidation is a pioneering synthesis technique for a structurally versatile class of terminal oxiranes.[36] The asymmetric version of CCR (*via* a chiral sulfide) has been developed over the past thirty years to complement alkene epoxidation.[7,37–41] The *retro*-Corey–Chaykovsky epoxidation involves the efficient transformation of epoxides to ketones in a non-oxidative and mildly basic environment.[42] The aza-Corey–Chaykovsky reaction was first reported by Aggarwal *et al.* as an efficacious carbenoid-addition approach to attain aziridines.[43,44] The modification in traditional aza-CCR not only addresses the limitations in ketimine aziridination but also provides a practical route for the development of complex amino acid derivatives, reinforcing the versatility of Corey's original approach in modern synthetic strategies.[45]

The synthesis of natural products has always been a challenging and interesting subject for synthetic researchers.[46–49] The CCR provides a simple yet versatile strategy to convert any ethylenic moiety and, further, to develop natural products and structurally complex compounds.[50–52] E. J. Corey and his research group developed many new synthetic substances with intricate organic frameworks. They also carried out the total synthesis of significant natural compounds that encouraged the development of organic syntheses in recent years.[53] The Corey–Chaykovsky reaction has been found to be involved in the generation of a variety of lactones,[54] heterocyclic compounds,[55] and functionalized furans[56] as well as in the remolding of

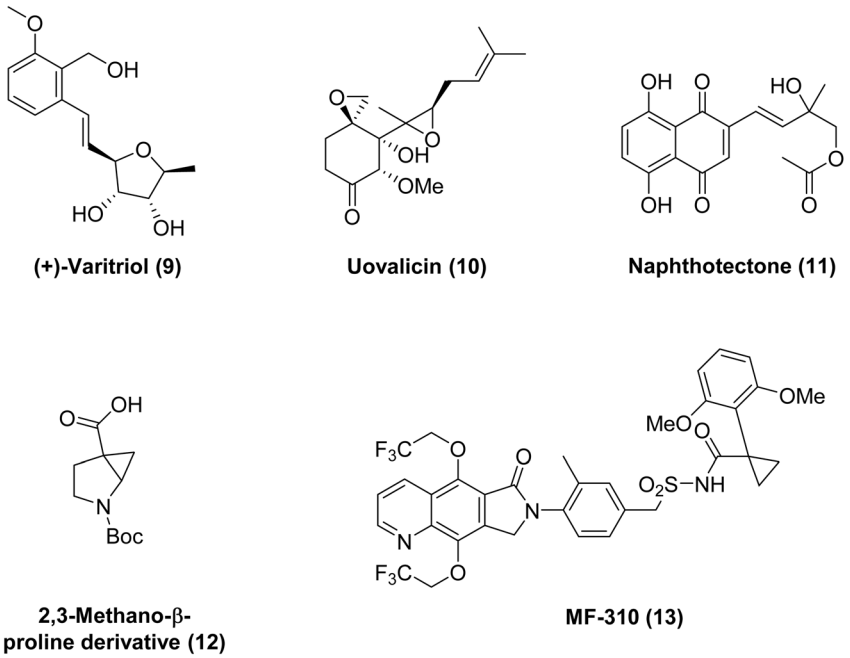


Fig. 2 Structures of natural products formed by employing the CCR as a key step.

pyridium salts.[57] The asymmetric CC cyclopropanation[58] also finds its applications towards the synthesis of dihydofurans and several new classes of hydrofluorenones.[59] In addition, asymmetrical intramolecular CC epoxidation has been reported to obtain vepdegestrant.[60] Till now, various natural products and synthetic analogs of natural products (aza-cryptophycin)[61] have been synthesized by incorporating the CCR as one of the significant steps, thereby highlighting its importance. Some of these bioactive natural products, such as (+)-varitriol **9**,[62] uovalicin **10**,[63] naphthotectone **11**,[64] 2,3-methano-β-proline derivative **12** (ref. 65) and MF-310 **13** (ref. 66) have been successfully synthesized by the CCR, whose structures are displayed in Fig. 2.

Altogether, the chemically stable and economical sulfur ylide reagents, regio and stereoselectivity, wide substrate scope, mild conditions, good yields and metal-free approach demonstrate the noteworthiness of the CCR for synthesizing various natural products. To date, only two reviews have been published featuring the applications of the CC cyclopropanation[67] and the methodological developments of the CCR, along with the total synthesis of natural products.[60] The purpose of our review is to highlight the recent applications of the Corey–Chaykovsky reaction as a pivotal step to access the diverse range of natural products reported since 2020.

2 Literature review

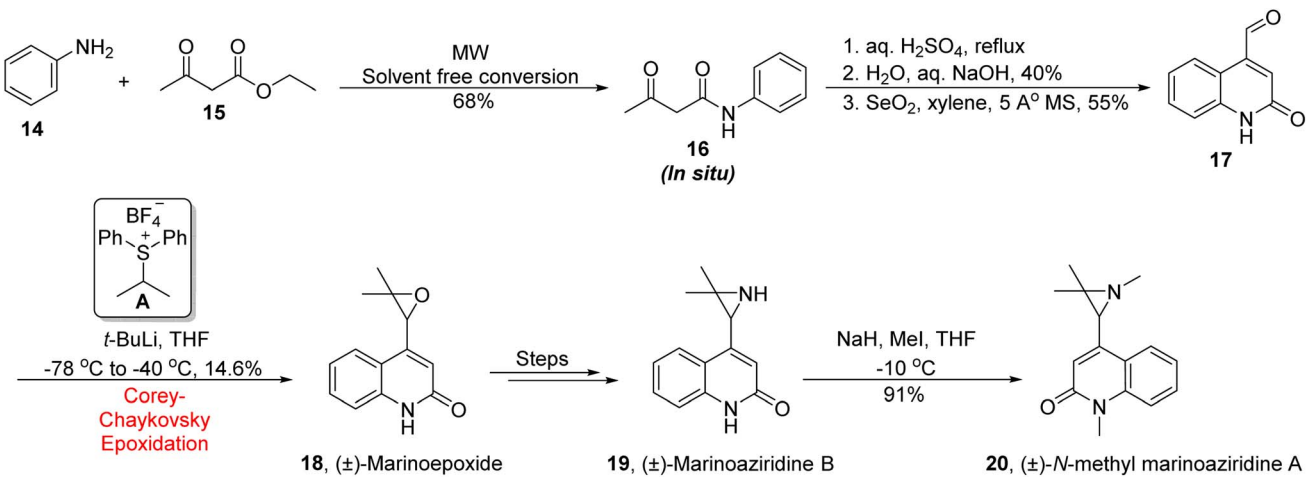
2.1. Synthesis of alkaloid-based natural products

The structures of two novel marine-derived chiral alkaloids, *i.e.*, marinoaziridine A and B, were isolated from the marine Gram-negative bacteria (Cytophagales order).[68] Marinoaziridines not only possess the therapeutically interesting quinolin-2(1*H*)-one ring but also the aziridine rings[69–71] featuring one stereocenter, allowing two enantiomers of each product. Both enantiomers are capable of exhibiting selective and distinct bioactivity.

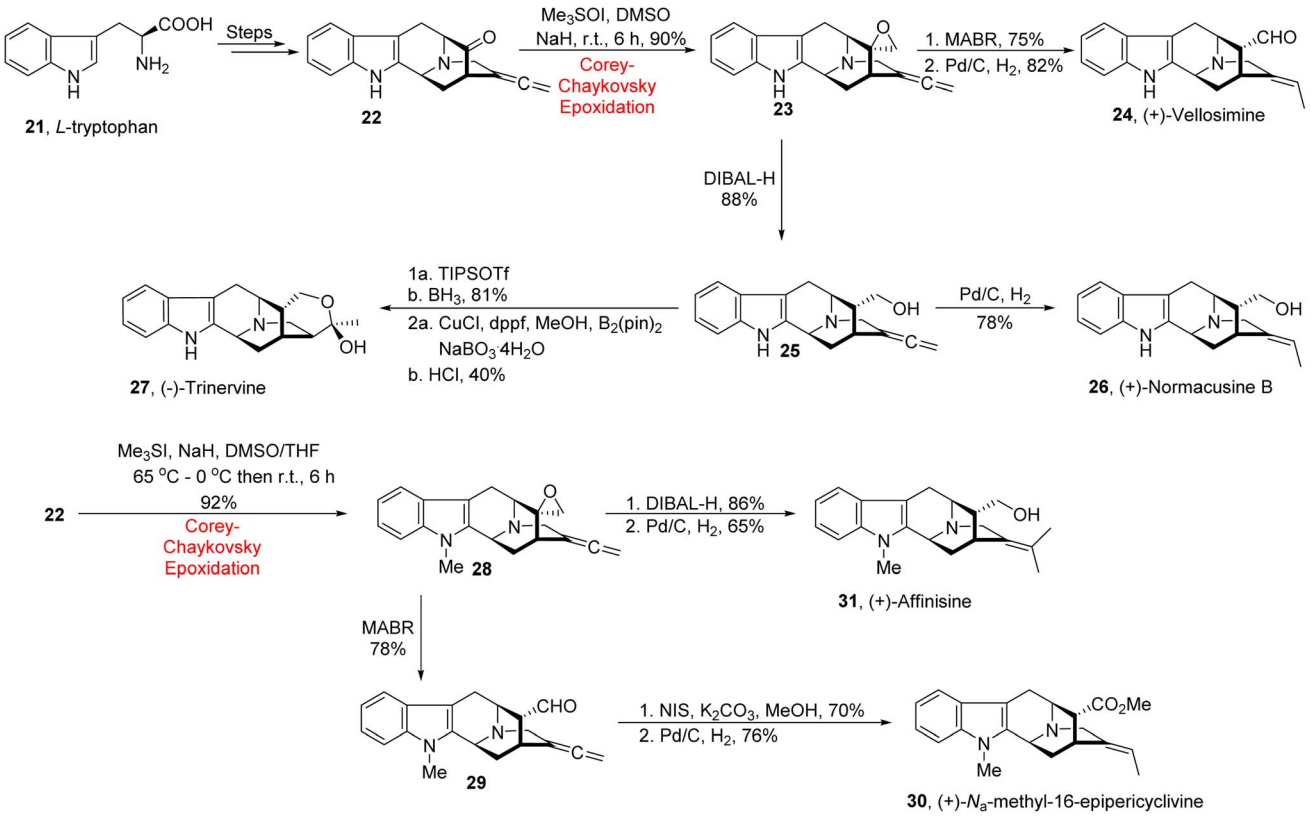
In 2024, Buljan *et al.*[72] reported the total synthesis of (±)-marinoaziridine B **19**, which involved the Staudinger reaction and the Johnson–Corey–Chaykovsky epoxidation as key steps.[73] Attempts to synthesize (±)-marinoaziridine A have not been successful so far, yielding only its (±)-*N*-methyl derivative **20**. Bulijan and coworkers explored the synthetic pathway involving the reaction of aniline **14** with ethyl acetoacetate **15** *via* microwave irradiation to furnish compound **16** in 68% yield, which in turn was subjected to the Knorr reaction, followed by Riley's oxidation[74] to accomplish aldehyde **17** in 55% yield. Moving forward, the Corey–Chaykovsky reaction between aldehyde **17**, sulfonium salt **A** (obtained by an $AgBF_4$-mediated reaction between 2-iodopropane and dimethyl sulfide[75]) and the *in situ* base-generated sulfur ylide, utilizing *t*-BuLi as the base in tetrahydrofuran, produced (±)-marinoepoxide **18** (at −78 °C to −40 °C) in 14.6% yield.[73] Consequently, the epoxide **18** was subjected to a multiple-step process to generate (±)-marinoaziridine B **19** in 80% yield, which was transformed into (±)-*N*-methyl marinoaziridine A **20** in 91% yield by utilizing MeI reagent and sodium hydride as the base (Scheme 2).

Sarpagine alkaloids are members of the monoterpene indole alkaloid family, mainly isolated from plant families (Apocynaceae and Gelsemiaceae).[76–80] Structurally, they are characterized by a cage-shaped core framework, involving indole-fused azabicyclo[2.2.2]octane and azabicyclo[3.3.1]nonane as substructures. Ajmaline, a notable analog of sarpagine alkaloid, is diagnostically used for Brugada syndrome.[81] Koumine alkaloids, originating from sarpagine alkaloids,[82,83] exhibit a wide range of analgesic, anti-tumor, immunomodulatory and anti-inflammatory properties.[84,85] However, the putative bioactivities of sarpagine alkaloids are yet to be explored, presumably because of their scarce nature.

In 2021, Yang *et al.*[86] strategically developed a unified total synthetic pathway for both Koumine and Sarpagine alkaloids, utilizing the Corey–Chaykovsky reaction as one of the key steps. Their strategy involved using L-tryptophan **21** (ref. 87) as a starting material for the construction of cage intermediate **22** in a multiple-step process, featuring allene and ketone groups. The assembly of a cage scaffold of intermediate **22** involves two structural transformations: (a) formation of the bicyclo[2.2.2] octane core *via* ketone α-allenylation and (b) construction of the



Scheme 2 Synthesis of (±)-marinoaziridine B **19**.

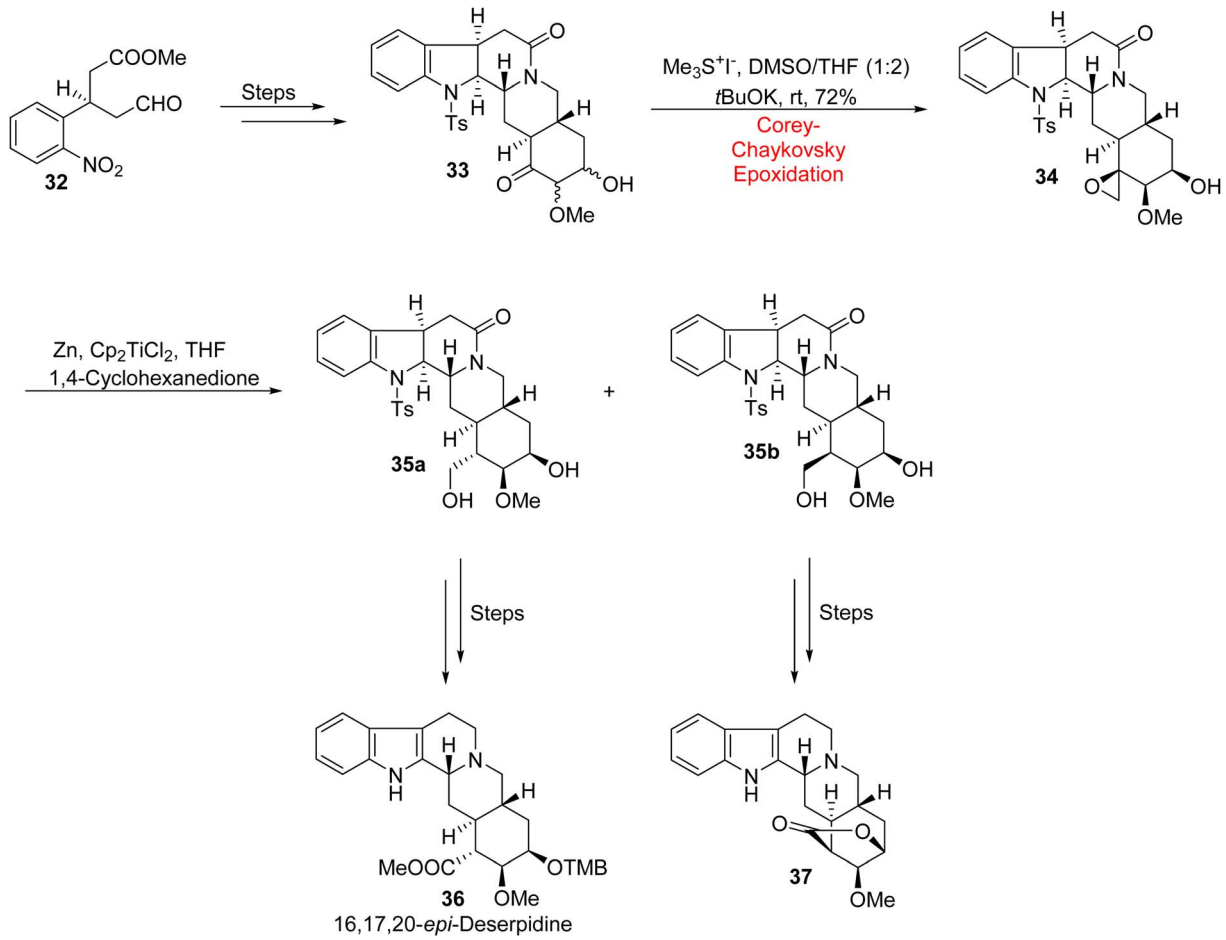


Scheme 3 Synthesis of sarpagine alkaloids.

bicyclo[3.3.1]nonane core through intramolecular oxidative cyclopropanol cyclization. Their strategy enabled the synthesis of a wide range of sarpagine alkaloids with different substituents after accessing the key precursor **22**. The intermediate **22** was subjected to the Corey–Chaykovsky reaction in the presence of Me_3SOI and sodium hydride in DMSO at room temperature for 6 hours to obtain epoxide **23** in 90% yield. Upon the treatment of epoxide **23** with MABR (methylaluminum bis(4-bromo-2,6-di-*tert*-butylphenoxide)), followed by partial allene hydrogenation, (+)-vellosimine **24** was afforded in good yield (>20 : 1 *E*/*Z* selectivities). Conversely, epoxide **23** was transformed into alcohol **25** (88%) by treating it with DIBAL-H, which was further converted into (+)-normacusine B **26** (>20 : 1 *E*/Z) by partial allene hydrogenation. However, the protection of the hydroxyl group and nitrogen atom of alcohol **25** as a borane-complexed silyl ether, the oxidation/hydrogenation of the allene moiety using Ma's protocol,[88] and silyl group deprotection and borane removal led to the preparation of (−)-trinervine **27** in 40% yield. Next, the Corey–Chaykovsky reaction of intermediate **22** with Me_3SI ylide, NaH in DMSO/THF (at 65 °C to 0 °C, then at rt, 6 h) afforded epoxide **28** in 92% yield, along with the addition of the –Me group on the indole nitrogen. Treating compound **28** with MABR produced compound **29** in 78% yield, which was further subjected to halogenation and partial hydrogenation to achieve (+)-N_a-methyl-16-epipericyclivine **30** in 76% yield.[89] Conversely, the reduction of **28** followed by partial hydrogenation afforded (+)-affinisine **31** in 65% yield (Scheme 3).

Reserpine and its congener deserpidine are significant Rauwolfia alkaloids that were extracted in the 1950s.[90–92] They have the potential to exhibit sedative and anti-hypertensive activities.[93] Both molecules are composed of a yohimbine scaffold and a highly functionalized cyclohexane ring; thus, the construction of these molecules poses a significant synthetic challenge. The total synthesis of naturally occurring deserpidine has rarely been reported compared to the case with reserpine,[94–99] and the only available asymmetric strategy involves the conversion of reserpines to deserpidine.[99] Wu and co-workers[99] accomplished the first asymmetric total synthesis of a stereoisomer of deserpidine in 2021 by employing a visible-light-induced radical cascade strategy[100] involving the Corey–Chaykovsky reaction as a significant step. To synthesize the deserpidine with a complete corynanthe scaffold, they aimed to assemble the tetracyclic ring system through the inter/intramolecular radical cascade reaction, which proceeded by ring formation.

The synthetic endeavor towards the total synthesis of deserpidine was commenced with the preparation of pentacyclic compound **33** as a pair of inseparable diastereomers (6 : 1) in 50% yield *via* a multiple-step approach from the chiral aldehyde **32**. For late-stage synthesis, the van Leusen reaction[101] failed to transform the ketone into a nitrile, generating an intermediate in only 24% yield. Therefore, the Corey–Chaykovsky reaction was performed with compound **33** by utilizing Me_3SI and *t*BuOK in the presence of a solvent at room



Scheme 4 Synthesis 16,17,20-*epi*-deserpidine **36**.

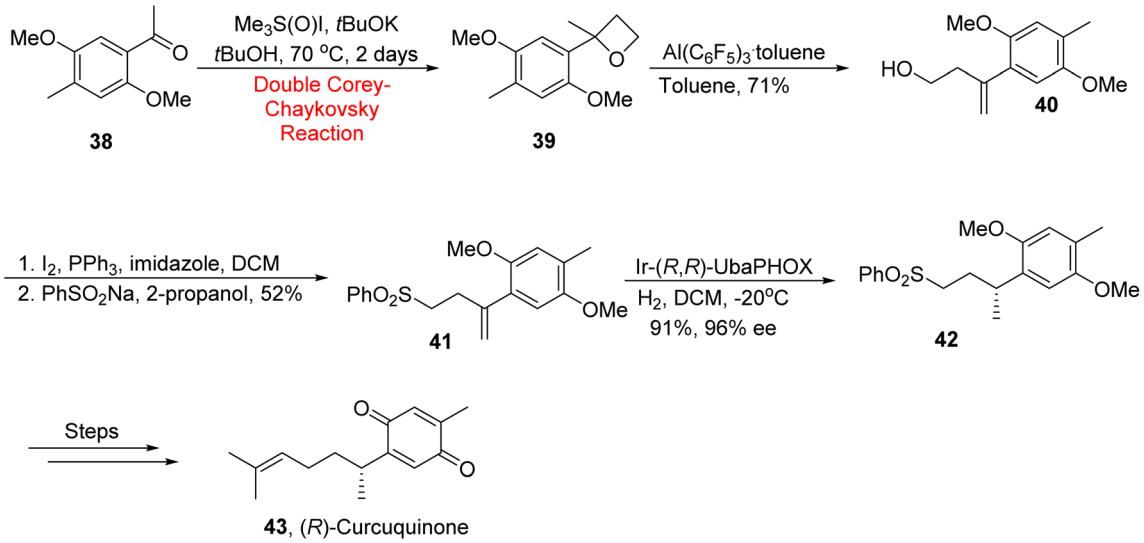
temperature, which resulted in epoxide **34** (72%, confirmed by X-ray). Subsequently, the epoxide **34** underwent reductive ring opening to afford separable diastereomers **35a** (65%) and **35b** (23%). Isomers **35a** and **35b** were subjected to a multiple-step approach to accomplish 16,17,20-*epi*-deserpidine **36** (69%) and a lactone derivative **37** (50%) of (−)-deserpidine, respectively (Scheme 4).

2.2. Synthesis of terpene-based natural products

2.2.1. Synthesis of sesquiterpenoid-based natural products. (*R*)-Curcuquinone **43** is a member of the bisabolene family of sesquiterpenes exhibiting anti-fungal and anti-microbial properties. In 2024, Bellido *et al.*[102] documented the enantioselective formal synthetic route to (*R*)-curcuquinone **43** to illustrate the applicability of an improved methodology for the regioselective ring opening of oxetane utilizing Lewis superacid $Al(C_6F_5)_3$. Their strategy featured the Ir-catalyzed asymmetric hydrogenation approach *via* the Ir-UbaPHOX ligand[103] to induce chirality and a double Corey–Chaykovsky reaction to synthesize the key intermediates,[104] which were pivotal for the synthesis of targeted natural products.

The seven-step total synthesis of chiral curcuquinone **43** began with the conversion of the acetophenone **38** to *p*-methoxyphenyl oxetane **39** *via* a double Corey–Chaykovsky reaction employing trimethylsulfoxonium iodide and *t*-butoxide in the presence of *t*-BuOH at 70 °C for 2 days to afford the oxetane **39**. Proceeding, the highly selective homoallylic alcohol **40** was achieved in 71% yield by the $Al(C_6F_5)_3$-catalyzed regioselective ring opening of oxetane **39** in toluene. Subsequently, homoallylic alcohol **40** was treated with iodine, triphenylphosphine and imidazole through the Appel reaction, followed by sodium phenyl sulfinate substitution to generate homoallylic sulfone **41** in 52% yield. The Ir-catalyzed asymmetric hydrogenation of sulfone **41** gave the enantioselective compound **42** (91%, 96% ee). Then, the enantioselective product **42** was processed through a few steps to give (*R*)-curcuquinone **43** in 10% overall yield (Scheme 5).

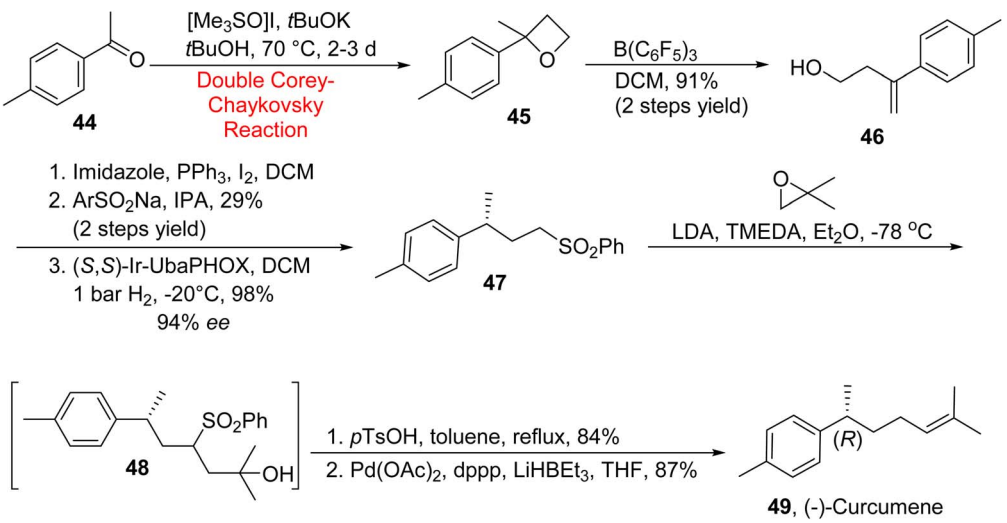
Curcumene **49** belongs to the bisabolane family of sesquiterpenes,[105,106] which displays a broad spectrum of bioactivities. They are widely recognized as traditional medicines[107,108] and exhibit distinct enantiomeric properties. In particular, (*S*)-α-curcumene is used as an insecticide, whereas (*R*)-α-curcumene exhibits anti-tumor and anti-microbial properties.[109,110] The stereogenic α-methyl aromatic moiety is the key feature of many natural products and pharmaceutical drugs. In 2023, Bellido *et al.*[110] described the method for the asymmetrical total



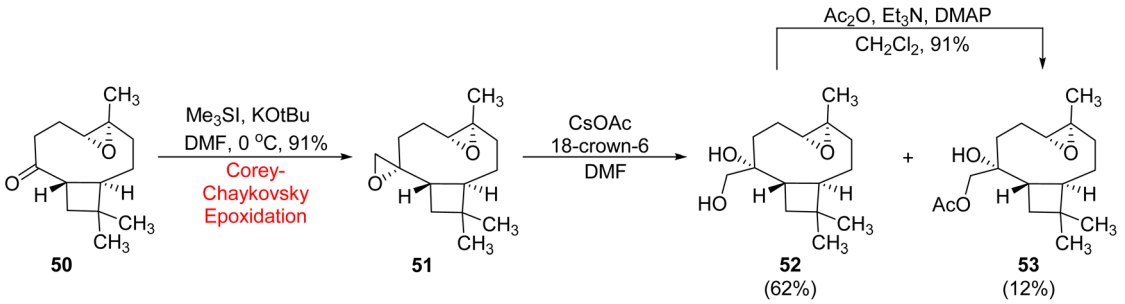
Scheme 5 Synthesis of (*R*)-curcuquinone (*R*)-**43**.

synthesis of (−)-curcumene **49**, involving the synthesis of homoallylic sulfones, Ir-catalyzed asymmetric hydrogenation and Corey–Chaykovsky reaction as pivotal steps. The homoallylic alcohols served as precursors for the synthesis of the corresponding homoallylic sulfones. In the foremost step, oxetane **45** was synthesized from aryl methyl ketone **44** *via* a double Corey–Chaykovsky reaction.[111] The $B(C_6F_5)_3$-catalyzed regioselective isomerization of oxetane **45** generated homoallylic alcohol **46** in excellent yield (91% yield),[112] and the Appel reaction and nucleophilic substitution reaction yielded homoallylic sulfones. Subsequently, the iridium-catalyzed asymmetric hydrogenation of homoallylic sulfones was studied by utilizing a substrate and Ir-Ubaphox catalyst {[(4*S*,5*S*)-Cy2-Ubaphox]Ir(COD)} BAr_F (C1),[113] to obtain γ-chiral sulfones. The reaction proceeded effectively at 1 bar H_2, with 93% ee yield obtained at room temperature.[114] By increasing pressure (15–50 bar), the enantioselectivity of the reaction reduced due to isomerization,[115] whereas it increased by lowering the temperature to −20 °C up to 97% ee. The α-deprotonation of γ-chiral sulfones utilizing LDA/TMEDA, followed by alkylation with 2,2-dimethyloxirane,[116] afforded **48** as a 2 : 1 mixture of diastereomers. The dehydration of **48** yielded an olefin under reflux conditions. In addition, the sulfone group was eliminated using a Pd-catalyzed methodology involving $LiHBEt_3$ (superhydride) under mild conditions,[117] thereby resulting in (*R*)-(−)-curcumene **49** in 72% yield (Scheme 6).

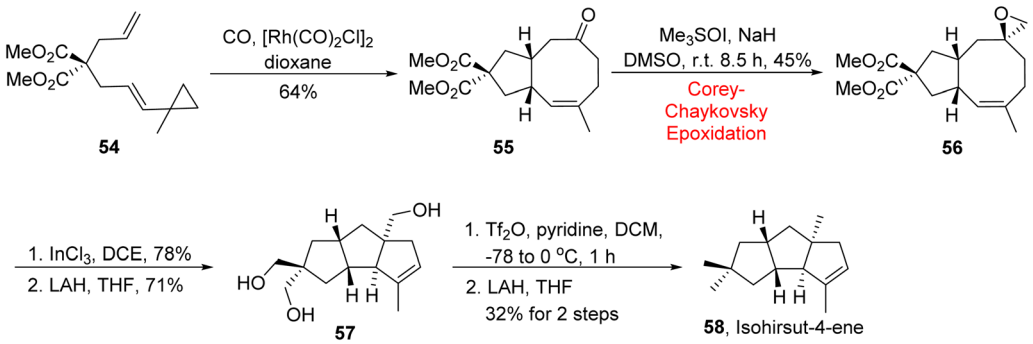
Linariophyllenes A–C were isolated from *Evolvulus linarioides*, which belong to the caryophyllane-type sesquiterpenoid family. The biosynthetic modifications of β-caryophyllene or its oxide result in the generation of these natural products. Linariophyllenes A–C have been found to exhibit anti-inflammatory properties, particularly linariophyllene B.[118] In 2023, Stakanovs *et al.*[119] developed a semisynthetic approach to synthesize linariophyllenes A–C by harnessing easily accessible



Scheme 6 Synthesis of (*R*)-(−)-curcumene **49**.



Scheme 7 Synthesis of linariophyllene C **53**.



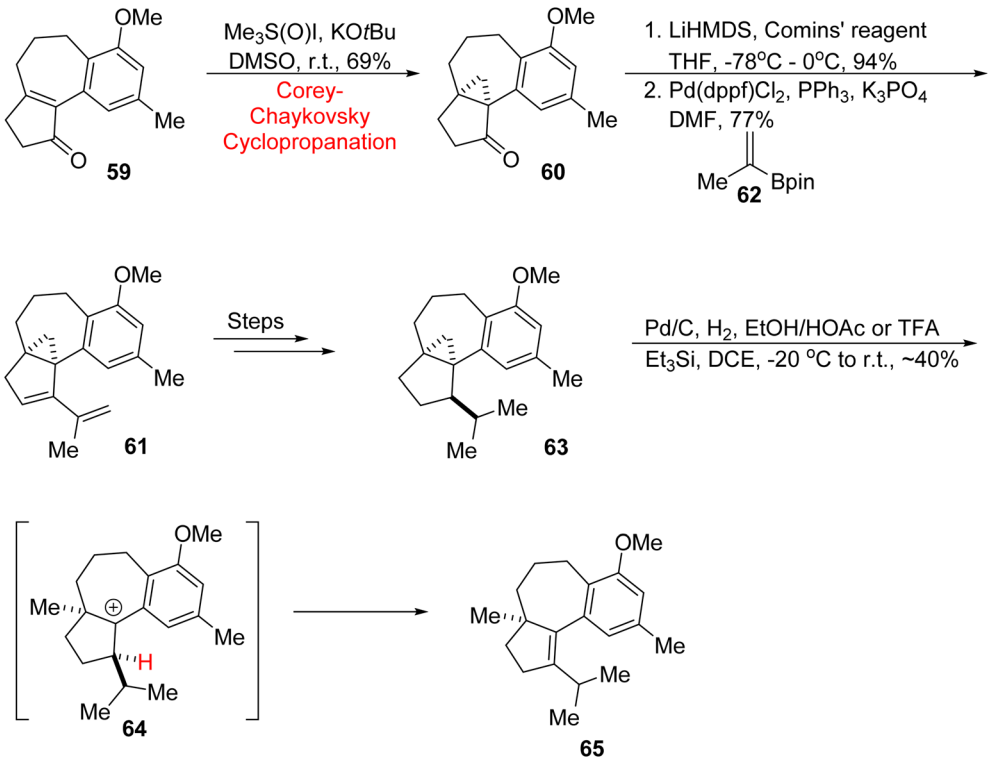
Scheme 8 Synthesis of isohirsut-4-ene **58**.

and cost-effective sesquiterpenoid starting materials.[120–125] The total synthesis of linariophyllene C employed Corey–Chaykovsky epoxidation as one of the significant steps. The synthesis commenced with the stereo-selective Corey–Chaykovsky epoxidation of kobusone **50** utilizing trimethylsulfonium iodide with KO*t*Bu as the base in DMF, at 0 °C to achieve diepoxide **51** in 91% yield and increased stereoselectivity. Subsequently, the ring opening of one of the epoxides of diepoxide **51** in the presence of CsOAc and 18-crown-6 at a high temperature produced the diol **52** as the main product in 62% yield and acetate **53** in 12% yield. The desired acetate **53** was also synthesized from diol **52** in 91% yield using a standard acetylation procedure (Scheme 7).

Isohirsut-4-ene **58** is a linear triquinane-based natural product characterized by tricyclic skeletons, which displays a wide range of biological properties. The synthesis of such triquinanes and their congeners could be noteworthy for pharmaceutical and biological research. Ikeda's group[126] isolated isohirsut-4-ene and isohirsut-1-ene from engineered bacteria. In 2022, Liu *et al.*[127] disclosed the first total synthesis of isohirsut-4-ene **58** with a 5/5/5 tricyclic core, confirming the proposed structure. Prior to this study, their structures had not been determined, and even Kutateladze[128] and Tantillo[129] had only predicted their relative configuration *via* computational NMR data. Liu and co-workers developed a new transannular strategy based on the [5 + 2 + 1] reaction[130–132] for linear triquinanes (isohirsut-4-ene). The synthesis featured a [5 + 2 + 1] cycloaddition, the Corey–Chaykovsky reaction, and a transannular epoxide–alkene cyclization to construct the key framework of a natural product.

The six-step total synthesis of **58** began with the preparation of starting compound **54**, *i.e.*, ene-VCP (DEC tethered ene-vinylcyclopropane)[133,134] in a single step. Then, the [5 + 2 + 1] reaction was carried out under optimized conditions to obtain a pure diastereomer of 5/8 bicyclic product **55** (64% yield). Compound **55** was then transformed into epoxide **56** (45% yield) *via* the Corey–Chaykovsky reaction under standard conditions (NaH, DMSO, trimethylsulfoxide iodide). A transannular epoxide–alkene cyclization of epoxide **56** utilizing the $InCl_3$ catalyst afforded a 5/5/5-fused tricyclic product, followed by the $LiAlH_4$-promoted reduction that resulted in a triol product **57** (71% yield). Compound **57** was converted into trifluoro-methanesulfonate ester, followed by the reduction of all three hydroxyl groups of esters *via* LAH, thereby furnishing the desired product, isohirsut-4-ene **58**, in 32% overall yield. The NMR spectral results of synthetic compound **58** were determined to be consistent with the literature data. The strategy was further extended to synthesize other congeners of linear triquinanes (Scheme 8).[135]

2.2.2. Synthesis of diterpenoid-based natural products. Hamigerans belong to the family of diterpenoids, displaying significant biological and structural activities. Cambie and his colleagues first isolated numerous hamigeran natural products from *Hamigera tarangaensis*.[136–140] This family structurally exhibits tricyclic cores of two types, 6–6–5 and 6–7–5, featuring a polysubstituted and brominated aromatic ring. *In vitro*, hamigeran B exhibits potent inhibitory action against the



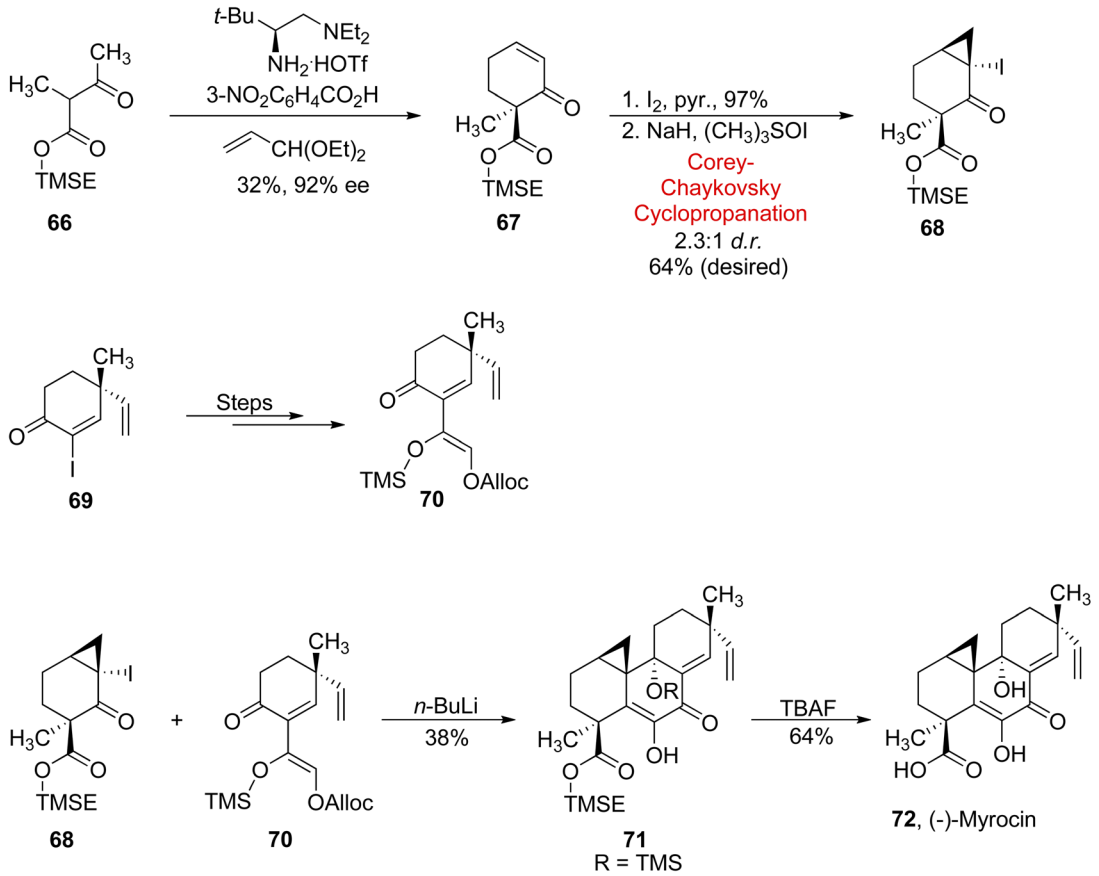
Scheme 9 Synthesis of compound **65**.

replication of polio and herpes virus, and hamigeran G 7 shows inhibition against the growth of HL-60 (leukemia) cell line. Early research focused on the 6–6–5 tricyclic core of hamigeran A and B, which led to several efficient total syntheses. However, the challenge of synthesizing seven-membered rings resulted in fewer reports focusing on the synthesis of hamigerans with a 6–7–5 carbon core.

In 2016, Gao *et al.* revealed the first total synthesis of hamigeran G by employing (*R*)-piperitone, followed by the Suzuki and McMurry coupling to afford a key intermediate.[141] Subsequently, in 2018, Stoltz and colleagues[142] reported the total syntheses of hamigeran C and D through a Pd-catalyzed asymmetric decarboxylative allylation and other key steps. In 2020, Jiang *et al.*[143] devised a synthetic strategy for the construction of a 6–7–5 three-cyclic carbon framework of hamigeran natural products. Their first attempt featuring 5-bromovanillin 144 as the starting material did not work out, as they were unsuccessful in reducing the tetrasubstituted double bond. In the second attempt, Jiang and his group envisioned the selective C–C bond cleavage of cyclopropane as a masked CH_3 group. Their synthetic route commenced with the Corey–Chaykovsky cyclopropanation[145] of symmetric tricyclic enone **59**, utilizing the trimethylsulfoxonium iodide reagent with KO*t*Bu base in DMSO at room temperature to afford tetracyclic compound **60** in 69% yield. Subsequently, compound **60** was transformed into vinyl triflate in 94% yield in the presence of Comin's reagent and LiHMDS in THF at −78 °C to 0 °C, followed by Suzuki coupling with **62** in DMF that resulted in diene **61** in 77% yield. Thereafter, the diene **48** underwent a sequence of steps to afford **63**, which was subjected to hydrogenation conditions in a mixture of CH_3COOH and ethanol or THF and triethylsilane in DCE to afford benzylic cation **64** initially due to the acidic conditions. Later, benzylic cation **64** was transformed into the desired product **65** in 40% yield *via* deprotonation. Although the saturation of the tetrasubstituted double bond of intermediate **65** and the selective cleavage of the C–C bond in cyclopropane **63** could not be achieved, the reported synthetic pathway led to the construction of a tricyclic carbon core (6–7–6) of hamigeran natural products (Scheme 9).

In 1989, myrocins were first discovered in culture filtrates of the soil fungus *Myrothecium verrucaria*, which belongs to the family of anti-proliferative and antibiotic pimarane diterpenes.[146,147] (+)-Myrocin C and (−)-myrocin B were the first isolated metabolites that showcased antibiotic effect towards Gram (+) bacteria, fungi and yeast.[148,149] The structural analogs of metabolite 5–7 were isolated from cultures of marine and soil fungi, and they exhibited comparable antibiotic effects.[150–153] In 1993, Danishefsky and Chu-Moyer unveiled the pivotal total synthesis of (±)-myrocin C.[154,155] Later, Yamada and co-workers presented their research regarding myrocin C.[156] Prompted by the hypothesis of Chu-Moyer–Danishefsky that myrocin C could crosslink DNA[157] and following the Hoffmann *et al.*[158,159] model, Tomanik and co-workers[160] reported the synthesis of (−)-myrocin G recently. In 2020, Tomanik *et al.*[161] documented the synthetic pathway for myrocin G, involving the Corey–Chaykovsky reaction as one of the key steps.

The total synthetic pathway of (−)-myrocin G includes the complex stereoselective fragment coupling–cyclization cascade

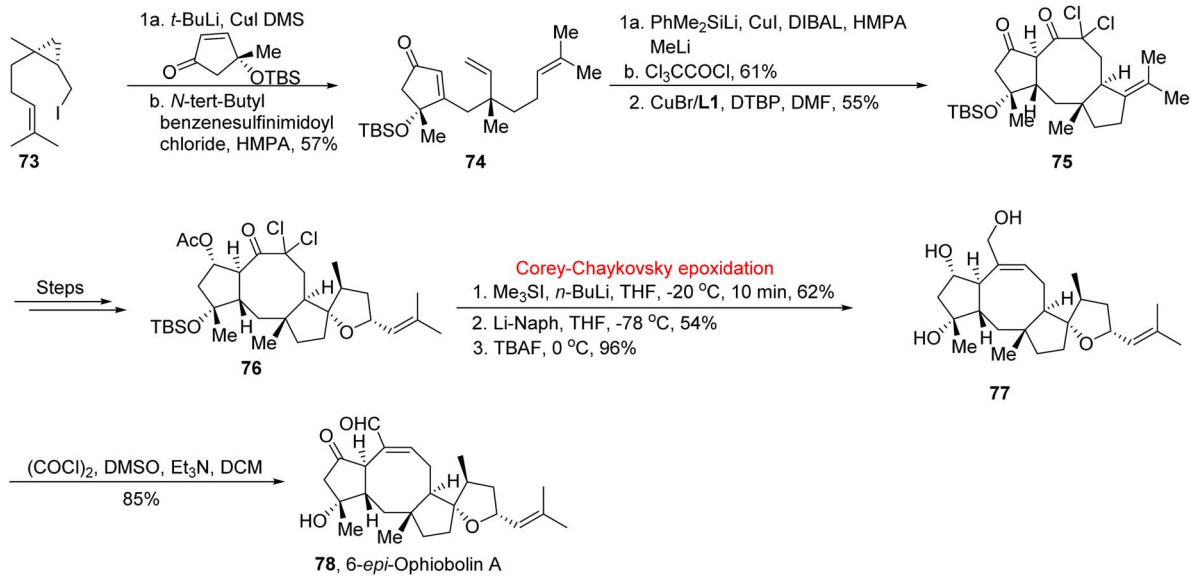


Scheme 10 Synthesis of (−)-myrocin G **72**.

of iodocyclopropane **68** and α-iodoenone **71**. In the first step, the preparation of iodocyclopropane **68** began with the asymmetric Robinson annulation[162] of the β-ketoester **66** with diethyl acrolein to afford an enone **67** (32%, 92% ee). Next, the enone **67** was subjected to dehydroiodination by the aid of I_2 and pyridine, followed by the Corey–Chaykovsky cyclopropanation employing trimethylsulfoxonium iodide and NaH base, which furnished the enantioenriched iodocyclopropane **68** (d.r. = 2.3 : 1) in 68% yield. Secondly, the unsaturated ketone **69** underwent a six-step process to prepare the C-ring coupling fragment **70** in 19% overall yield. Subsequently, the cyclodehydration (tandem coupling) of **68** and **70** resulted in the desired diosphenol **71** in 38% yield. Lastly, the global deprotection of **71** employing TBAF delivered the (−)-myrocin G **72** in 64% yield (Scheme 10).

2.2.3. Synthesis of sesterterpenoid-based natural products. The ophiobolins are bioactive 5,8,5-fused sesterterpene-based natural products that are extracted from fungal pathogens (*Aspergillus* and *Bipolaris* genus).[163–165] In particular, ophiobolin A **78** is highly cytotoxic against breast cancer (MCF-7), multidrug-resistant leukemia (MDR HL-60), glioblastoma multiforme (GBM) and thirty other cell lines. The 6-*epi*-ophiobolin A **78** epimer also exhibits cytotoxic activity, and a cell-line-specific relationship has been found between C6 stereochemistry and anti-cancer activity.

Regardless of the significance of ophiobolin in the synthetic community, only three ophiobolin syntheses were reported in the last 30 years before 2020.[166,167] Thach *et al.*[168] in 2020 introduced a 14-step pathway to (+)-**78**, utilizing a radical cascade approach. Their successful synthetic strategy expanded the synthesis of a number of key structural derivatives of ophiobolins. Thach's total synthesis commenced with the preparation of a geraniol-derived cyclopropyl iodide **73** (*via* Charette's protocol),[169,170] which was transformed into a ring-opened lithiate and was coupled with the (−)-linalool-derived enone **74**, resulting in an enolate intermediate. In the following step, the enolate was quenched with *N*-*tert*-butylbenzenesulfinimidoyl chloride (Mukaiyama's reagent), forming the corresponding enone **74** directly.[171] The highly selective 1,4-reduction enabled by $PhMe_2SiCu$–H and *C*-acylation with Cl_3CCOCl, followed by radical cyclization *via* di-*tert*-butylbipyridine-ligated Cu, afforded the polycycle **75** in 55% yield on isolation. Compound **75** then underwent a sequence of reactions to ultimately yield the *trans*-addition product **76**. Compound **76** was further treated *via* four steps involving a final approach to accomplish the total synthesis of 6-*epi*-ophiobolin A **78**. The treatment of carbonyl C7 of **76** with Me_3SI and *n*-BuLi at −20 °C for 10 min generated the Corey–Chaykovsky epoxide in the presence of THF, followed by tandem reductive epoxide opening, dehalogenation and silyl ether deprotection (TBAF), which produced the triol intermediate **77** (52% yield). Lastly, the Swern oxidation of intermediate **77** afforded the 6-*epi*-ophiobolin A **78** in 85% yield (Scheme 11).



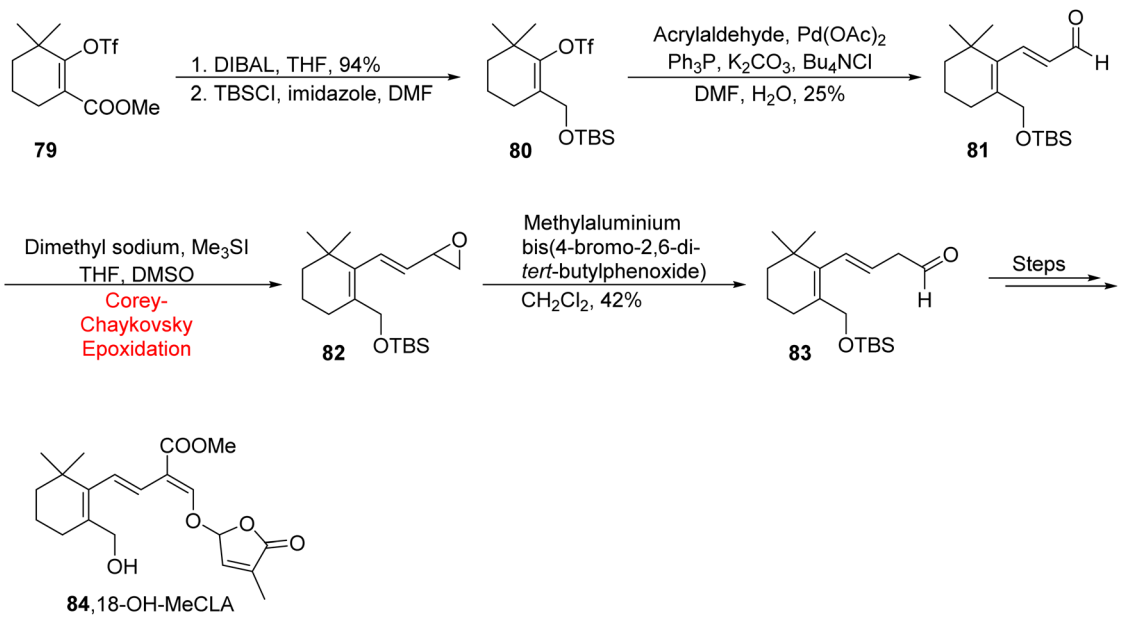
Scheme 11 Synthesis of 6-*epi*-ophiobolin A **78**.

2.2.4. Synthesis of apocarotenoid-based natural products. Strigolactones (SLs) (apocarotenoid compounds) are recognized as germination enhancers of root parasitic plants.[172] They also show application potential as rhizosphere-signaling compounds for the AM (arbuscular mycorrhizal) symbiotic relationship.[173,174] To date, about thirty strigolactones have been characterized from several plant root secretions.[175]

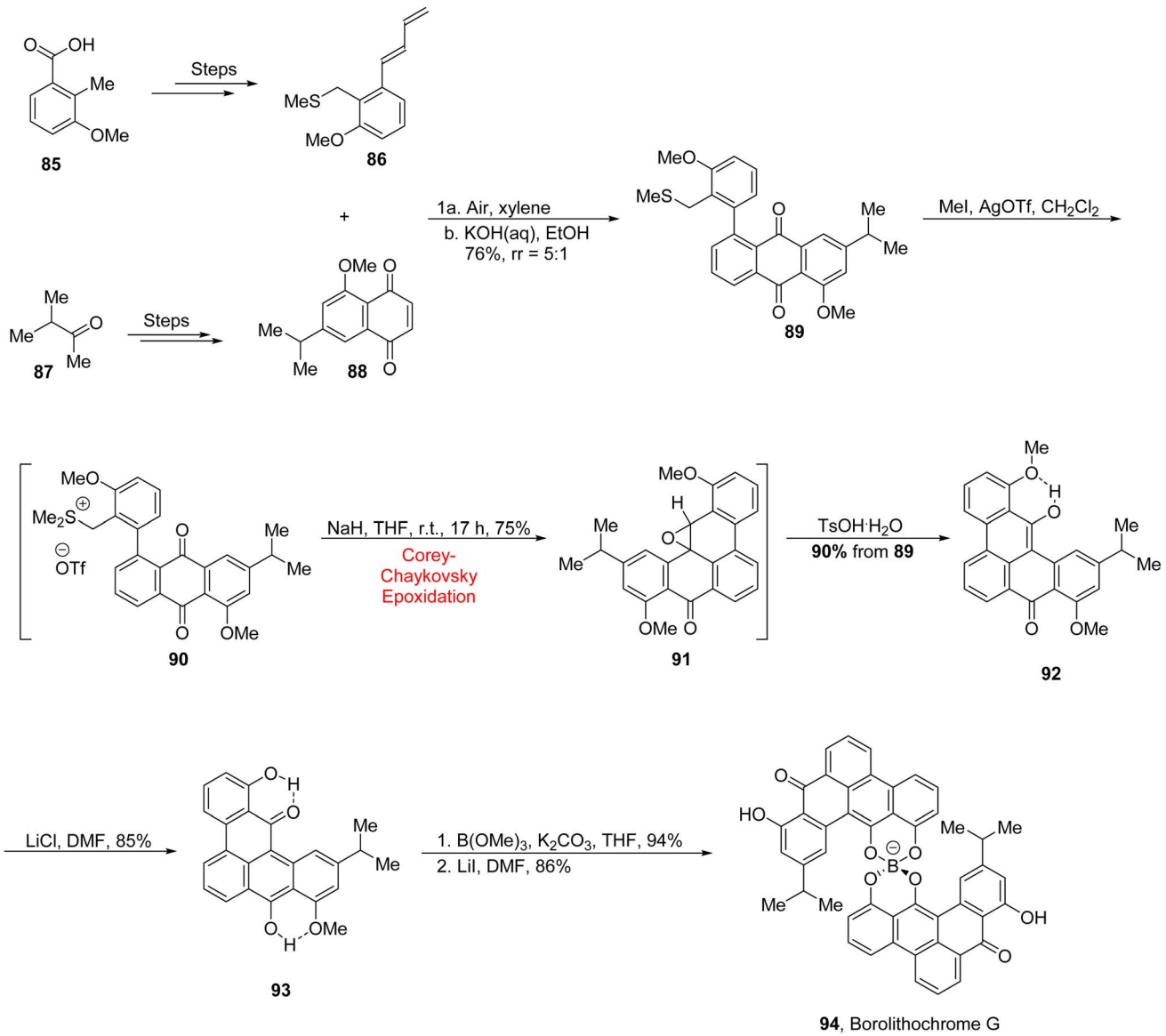
In 2020, Mori *et al.*[176] successfully synthesized 18-OH-MeCLA **84** in eight steps, including the Corey–Chaykovsky as a pivotal step in the synthetic route. The synthesis began with the triflate ester **79**, which was reduced with diisobutylaluminium hydride to give triflate alcohol, followed by the protection of the –OH group by a TBS [*tert*-butyl(dimethyl)silyl] group to obtain the resulting silyl-protected triflate **80**. The Heck reaction of silyl-protected triflate with acrolein afforded TBSO-C12-aldehyde **81**. The silylated aldehyde **81** was treated further to attain TBSO-C13-aldehyde **82** *via* the Corey–Chaykovsky epoxidation upon reaction with dimethylsulfonium methylide and THF in DMSO, followed by MABR (methylaluminium bis(4-bromo-2,6-di-*tert*-butylphenoxide))-promoted epoxide rearrangement to afford aldehyde **83**. The aldehyde in the multiple-step process afforded 18-OH-MeCLA **84** (Scheme 12).

2.3. Synthesis of polyketide-based natural products

Borolithochromes are rare natural products composed of unique spiroborate cores, featuring two benzo[*gh*]tetraphene



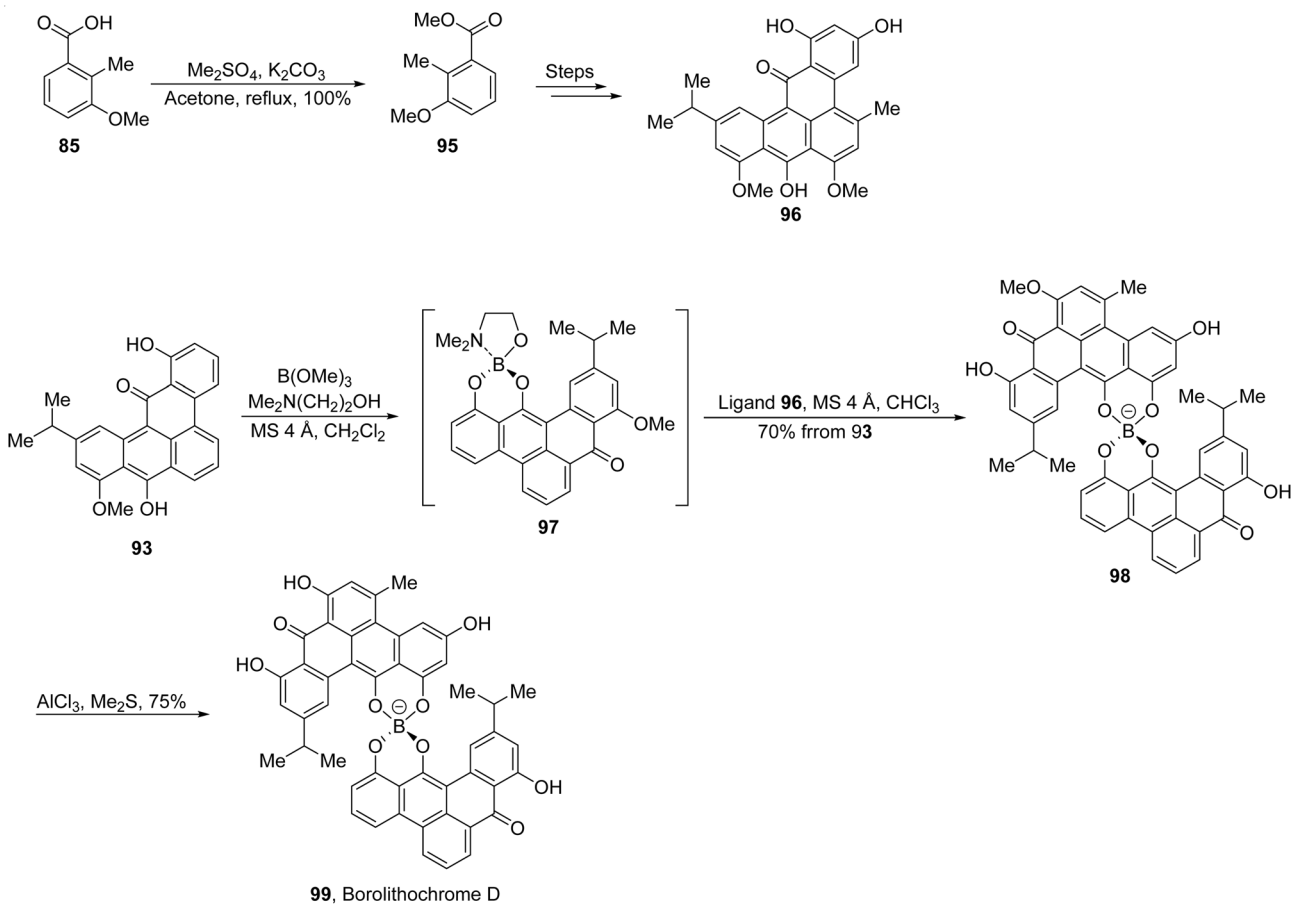
Scheme 12 Synthesis of 18-OH-MeCLA **84**.



Scheme 13 Synthesis of borolithochrome G **94**.

ligands.[177] These red pigments have been isolated from the remains of *Solenopora jurassica*[178] (Jurassic putative red alga). From this family, a racemic mixture of borolithochromes A, D, and G was isolated, whereas borolithochrome F was attained as a single enantiomer. Furthermore, the benzo[*gh*]tetraphene scaffold is rarely found in natural products, barring clostrubins A and B, which exhibit potent anti-bacterial properties.[179,180] Likewise, it was expected that the ligands in borolithochromes also exhibit bioactivities. Due to the limited availability of isolated borolithochromes, the information regarding their bioactivities and notable structures was scarce, motivating scientists to develop the total synthesis methods for these pigments.

In 2024, Kirita *et al.*[181] carried out the first total syntheses of borolithochromes A, D and G involving the Diels–Alder reaction for tricyclic intermediates, intramolecular Corey–Chaykovsky reaction to construct pentacyclic ligand and spiroborate formation as one of the significant steps. Firstly, the synthetic route for borolithochrome G **94** involved the Diels–Alder reaction. The desired diene **86** and dienophile naphthoquinone **88** were prepared individually *via* a multiple-step approach using benzoic acid derivative **85** and isopropyl methyl ketone **87** as starting materials, respectively. Then, treating diene **86** and naphthoquinone **88** *via* the Diels–Alder reaction resulted in the formation of an anthraquinone **89** mixture (5 : 1) in 76% yield. In the next step, the mixture produced the sulfonium ion **90** on treating it with iodomethane. The sodium hydride was added at r.t. to the solution of sulfonium ion **90** in dry THF to facilitate the intramolecular Corey–Chaykovsky epoxidation, which afforded the pentacyclic epoxide **91** in 75% yield. The crude mixture **91** was rearranged under acidic conditions to give phenol **92** in 90% yield. Ultimately, the phenol **92** (ref. 182) was



Scheme 14 Synthesis of borolithochrome D **99**.

subjected to multiple steps, resulting in the targeted natural product, borolithochrome G **94**, in 86% yield (Scheme 13).[183]

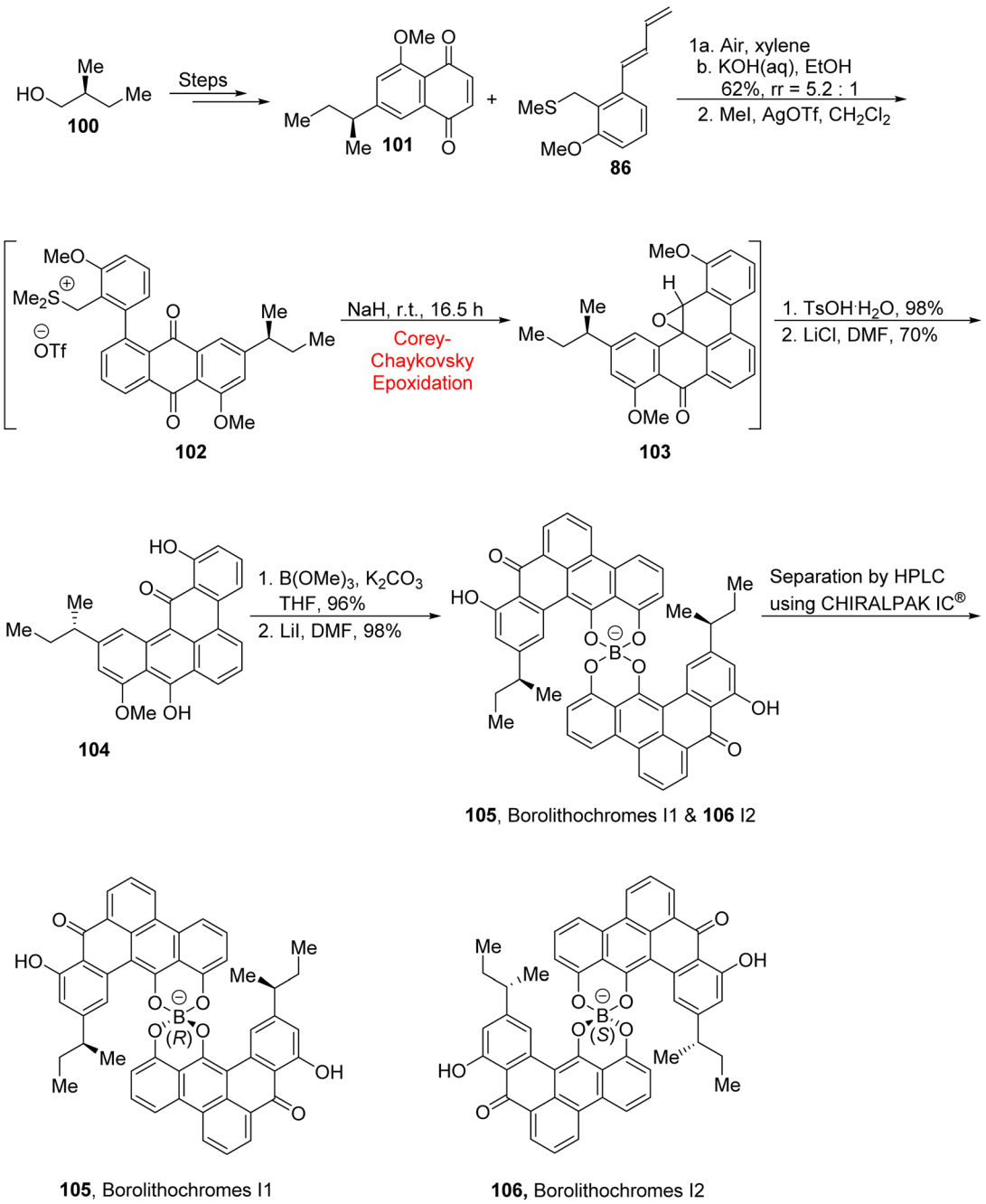
The spiroborate of borolithochrome D (**99**) also consists of ligands of borolithochrome A and D. Thus, the synthesis of a heterocomplex was achieved by the stepwise substitution of ligands in borate, which involved the boron : aromatic (1 : 1) ligand complex intermediate. The synthesis involved the coupling of ligands **93** (obtained *via* Corey–Chaykovsky reaction) and **96**. Initially, the monomer complex **97** was prepared by treating ligand **93** with trimethyl borate in the presence of *N*,*N*-dimethylethanolamine. Then, the ligand **96** was complexed with **97** to form a mixed complex, which was further subjected to *O*-demethylation using $AlCl_3$ to afford the borolithochrome D **99** in 75% yield (Scheme 14).

In 2024, Kirita *et al.*[184] first reported the method for the total syntheses of optically pure borolithochromes I1 (**105**) and I2 (**106**) involving the Diels–Alder reaction, Corey–Chaykovsky reaction and boron complexation as key steps. The synthetic route began with the synthesis of a common pentacyclic ligand. Firstly, the naphthoquinone **101** was prepared from (*S*)-2-methylbutanol **100** *via* TEMPO oxidation[185] in six steps. Subsequently, the naphthoquinone **101** and diene **86** were subjected to the Diels–Alder reaction under basic conditions to give the product in 62% yield, followed by *S*-methylation to give sulfonium ion **102**. NaH was added to the sulfonium ion **102** in dry THF at r.t. to facilitate the intramolecular Corey–Chaykovsky epoxidation,[186] which gave the pentacyclic epoxide **103** in 75% yield. The epoxide **103** then underwent rearrangement[187] and gave the product in 98% yield, followed by C-selective *O*-demethylation with LiCl in DMF, which resulted in the pentacyclic ligand **104** in 70% yield.[188,189]

Moving forward, the monomethyl ether **104** was treated with $B(OMe)_3$ in potassium carbonate to give the product in 96% yield, followed by *O*-demethylation *via* LiI in DMF to produce the mixture of borolithochromes I1 (**105**) and I2 (**106**) in 98% yield.[182] Ultimately, the diastereomeric mixture was separated by HPLC *via* CHIRALPAK IC to give optically pure borolithochrome I1 **105** and I2 **106** (Scheme 15).

2.4. Synthesis of cyclic depsipeptide-based natural products

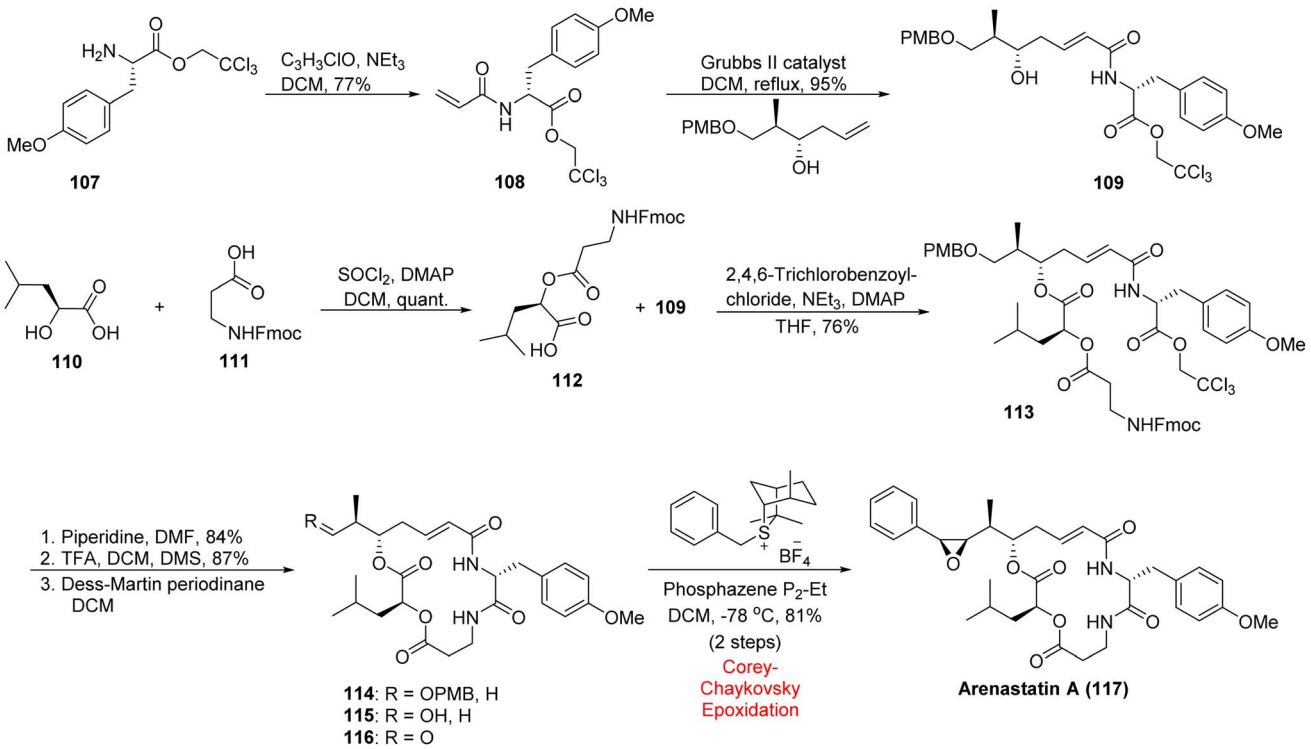
Arenastatin A is a cytotoxic cyclic depsipeptide, first isolated from *Dysidea arenaria* Okinawan marine sponge in 1994.[182] Total synthesis and NMR analyses have been employed to determine its structure.[190,191] Depsipeptides are members of the cryptophycin family that display potent cytotoxic behavior.[192] Cryptophycin-52, a powerful analog, was discovered by extensive medicinal research. The cytotoxicity of arenastatin A and its related analogs is influenced by the stereochemistry of the



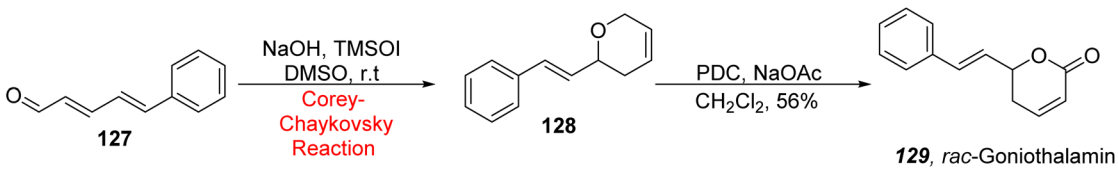
Scheme 15 Synthesis of borolithochrome I1 **105** and I2 **106**.

compounds. The 7,8-epoxide moiety is crucial in the compounds, as its (7*S*,8*S*) epimer is inactive. Previously, this moiety was achieved either *via m*-CPBA/dioxirane oxidation or cyclization of bromohydrin, which resulted in isomeric mixture that required separation and relatively long synthetic routes, respectively. However, Aggarwal *et al.*[193] devised an efficacious technique to construct a stereoselective epoxide (>99 : 1 d.r.) moiety *via* CCR using the chiral sulfonium salt.

In 2024, Mihara *et al.*[194] proposed an optimized synthetic route for the total synthesis of arenastatin A **117** and analogs of segments B, including the construction of the 7,8-epoxide moiety using the Corey–Chaykovsky reaction. The synthetic route began with the assembly of the four segments A–D. Firstly, (*R*)-*O*-methyltyrosine **107** was transformed into an acrylamide (77%) using C_3H_3ClO and NEt_3 in DCM. The acrylamide went through cross-metathesis with segment A, employing Grubbs II catalyst on reflux, producing segment AC **109** (95%). On the other hand, Fmoc-β-alanine **111** (segment D) was coupled with L-leucic acid **110** using $SOCl_2$ and acyl chloride (segment B) to give the segment BD **112**. Then, the assembly of two segments following the Yamaguchi esterification technique resulted in the cyclization of precursor **113**, which, on Fmoc removal with



Scheme 16 Synthesis of arenastatin A **117**.



Scheme 17 Synthesis of *rac*-goniothalamin **129**.

piperidine[195] and macrocyclization, led to macrolactam **114** (84%). Lastly, the PMB was subjected to cleavage *via* TFA, followed by the Dess–Martin oxidation to afford the aldehyde **116.** The treatment of aldehyde **116** with a chiral sulfonium salt *via* the Corey–Chaykovsky epoxidation using phosphazene P_2–Et in DCM at −78 °C produced arenastatin A **117** in 81% yield, with complete stereoselectivity (Scheme 16).

2.5. Synthesis of styryl-lactone-based natural products

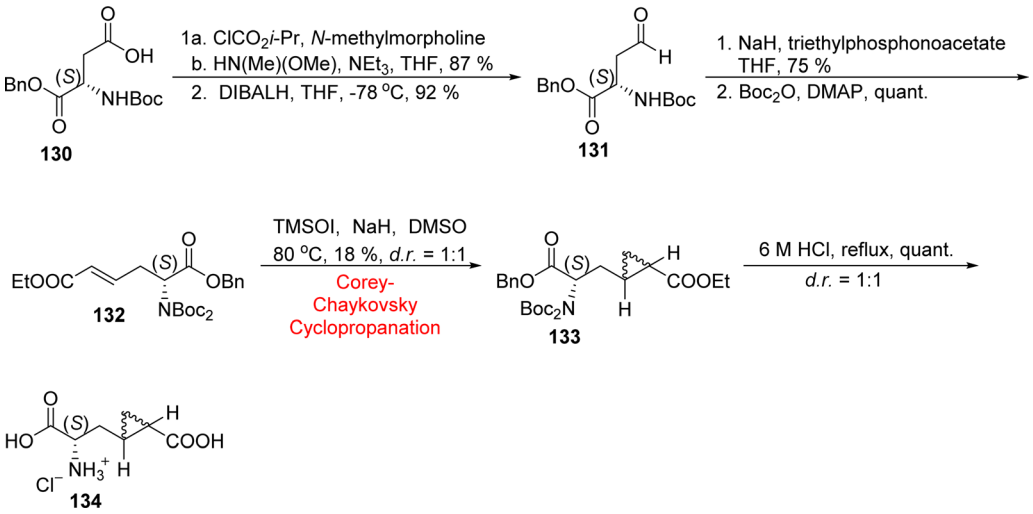
5,6-Dihydro-2*H*-pyran-2-one, 3,6-dihydro-2*H*-pyran (DHP) and tetrahydropyran (THP) are six-membered oxygen heterocycles, which are ubiquitous core units of a variety of natural products. *R*-(+)-Goniothalamin **129**, a 5,6-dihydro-2*H*-pyran-2-one derivative, exhibits cytotoxic properties. In 2022, Kumar *et al.*[196] reported a transition-metal-free approach to generate 3,6-dihydro-2*H*-pyran derivatives *via* a modified Corey–Chaykovsky reaction. It involved the synthesis of the desired epoxy cyclopropane from corresponding enones.

The two-step synthesis of racemic goniothalamin **129**, an anti-tumor agent, commenced with a styryl-substituted α,β-unsaturated aldehyde **127**, which was subjected to an extended Corey–Chaykovsky reaction using the sulfoxonium ylide and sodium hydroxide in DMSO to afford **128** at room temperature. Following this, compound **128** underwent oxidation to yield **129** (5,6-dihydro-2*H*-pyran-2-one) in the presence of PDC and sodium acetate in DCM (Scheme 17).

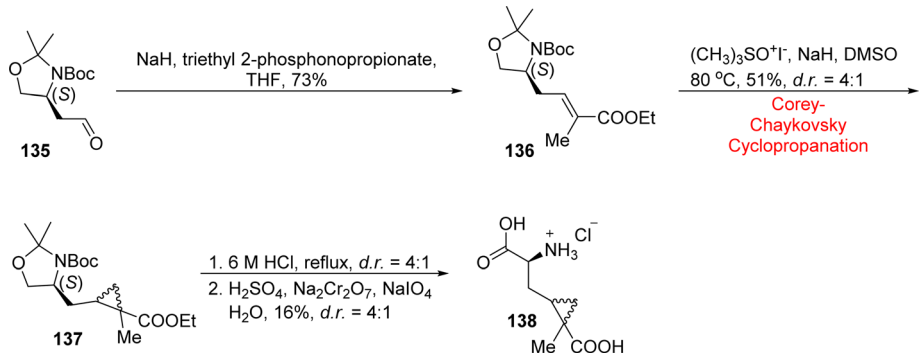
2.6. Synthesis of amino acid-based natural products

(2*S*)-Aminoadipic acid (AA), a homologue of (*S*)-glutamate, is a broad-spectrum endogenous agonist of mGluR. Madsen and co-workers[197] reported (*S*)-AA as a potent selective agonist for mGlu2. In 2024, Staudt *et al.*[198] documented their strategy to synthesize conformationally restricted hybrid structures of (*S*)-AA analogs. The synthetic route of these analogs featured a Corey–Chaykovsky reaction as one of the crucial steps.

The synthesis of (*S*)-AA analog **134** was initiated by the strategic protection of (*S*)-aspartate **130** to achieve Weinreb-amide, which was subjected to selective reduction to yield the desired aldehyde **131** in 92% yield. The Horner–Wadsworth–Emmons reaction of aldehyde **131** resulted in the *E*-isomer of unsaturated



Scheme 18 Synthesis of (*S*)-AA analog **134**.



Scheme 19 Synthesis of the 5-methyl analog **138**.

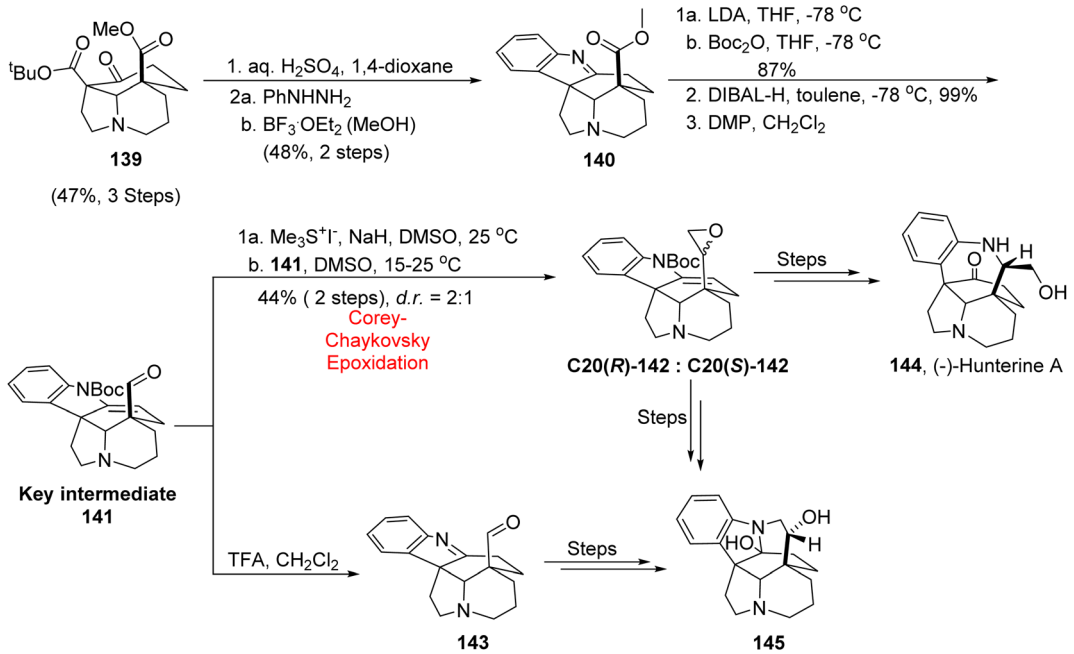
ester, followed by the double Boc-protection of the amine with DMAP to yield **132**. The *in situ* Corey–Chaykovsky reaction of **132** was carried out employing $(CH_3)_3SOI$ and sodium hydride to afford a 1 : 1 mixture of **133** in DMSO at 80 °C in 18% yield. Ultimately, the global deprotection of **133** in 6 M HCl on reflux resulted in the desired (*S*)-AA analog **134** with a 1 : 1 mixture of diastereomers (Scheme 18).

The synthesis of the 5-methyl analog **138** began with the olefination of commercially available aldehyde **135**, utilizing triethyl 2-phosphonopropionate and NaH, in the presence of THF to furnish the single stereoisomer of compound **136** in 73% yield. Subsequently, the Corey–Chaykovsky reaction of **136** was carried out to accomplish a 4 : 1 diastereomeric mixture of the 5-methyl-cyclopropane analog **137** in 51% yield employing TMSOI, sodium hydride and DMSO at 80 °C. Lastly, the global deprotection of analog **137** in 6 M HCl under reflux, followed by Jones-oxidation, afforded the desired analog **138** in 16% yield (4 : 1 d.r.) (Scheme 19).

2.7. Synthesis of hybrid natural products

2.7.1. Monoterpene indole alkaloids. In 2019, Zhang and colleagues[199] first isolated (−)-hunterine A **144** from *Hunteria zeylanica*, which belongs to the terpenoid indole alkaloid class with a characteristic 6/7/6/6/5 pentacyclic framework featuring an exotic 7-membered 2,3,4,5 tetrahydro-1*H*-azepine bridge scaffold.[200–202] The sparse amount of available alkaloid optimistically described the bioefficacy of (−)-hunterine A, which exhibited cytotoxicity against HepG2.[199] Zhang *et al.* reported a feasible biogenetic route for the synthesis of **144** using tuboxenine as the starting material.

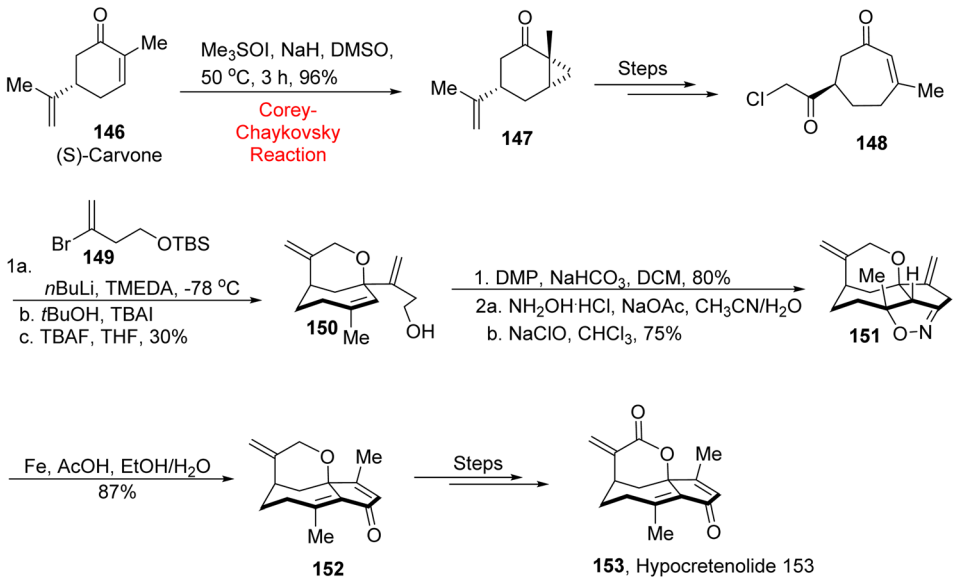
In 2024, Zsigulics *et al.*[203] pursued the bioinspired total synthesis of (−)-hunterine A (**144**) by addressing the selectivity challenges *via* the aspidosperma core unit. The total synthesis was achieved through an interim template technique carried out without a direct group, featuring the ring-opening cascade and the Corey–Chaykovsky reaction as critical steps to construct the epoxide intermediate. The bioinspired synthesis began with the modified Stork's tricyclic ketone **139**, which was subjected to selective hydrolysis and decarboxylation under acidic conditions, followed by Fischer indolization that produced indolenine **140** in 48% yield (2 steps). Then, the Boc-protection of indolenine **140** after deprotonation with LDA at −78 °C gave the product in 87% yield. Next, the partial reduction of the ester moiety in 2 steps (reduction *via* DIBAL-H in toluene at −78 °C



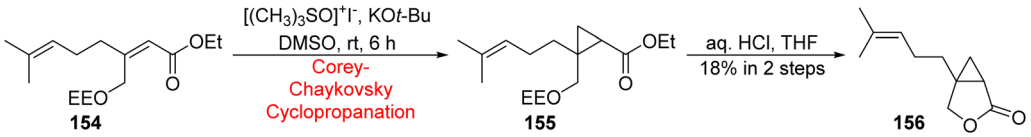
Scheme 20 Synthesis of (−)-hunterine A **144**.

with 99% yield, followed by oxidation *via* DMP in DCM) resulted in the key aldehyde intermediate **141**. Subsequently, the Corey–Chaykovsky reaction[204,205] was used to achieve the desired epoxide configuration by treating key intermediate **141** with $Me_3{}^+SI^-$ and sodium hydride in DMSO at 25 °C, followed by the addition of **141** in DMSO at 15–25 °C, resulting in **C20(*R*)-142** (d.r. = 1 : 2) in 44% yield (2 steps). Then, the **C20(*R*)-142** diastereomeric mixture was treated with aq. H_2SO_4 under biphasic conditions (DCM/water), inducing a sequence of cascade transformations, including protecting-group removal/hydration/epoxide ring opening as well as ring-expansion reactions, thereby ultimately resulting in (−)-hunterine A **144** alongside isomer **145**. Meanwhile, the key intermediate **141** was treated with trifluoroacetic acid in DCM to furnish aldehyde **143**. Thus, the isomeric product **145** was obtained as a single diastereomer by the C1 homologation of aldehyde **143** under cryogenic conditions using nucleophilic carbenoid, followed by exposure to acidic/hydrolytic conditions (Scheme 20).

2.7.2. Synthesis of sesquiterpene-lactone-based natural products. Hypocretenolides are naturally occurring sesquiterpenoids, first reported by Bohlmann *et al.* in 1982 from *Hypochaeris cretensis*.[206] A number of natural hypocretenolides



Scheme 21 Synthesis of hypocretenolide **153**.



Scheme 22 Synthesis of the analog of damascenolide™ **156**.

with variable glycosylation or oxidation states have also been isolated. Hypocretenolides feature an α-methylene-γ-lactone core exhibiting a distinct bridged 5/7/6 ring system. Prior research confirmed that these natural products are active against cancer metastasis[207,208] as they depicted low IC_{50} values against multiple tumor cell lines and suppressed the activation of NF-κB.[209,210] Regardless of the potential efficacy of hypocretenolides, further evaluation had been hindered due to their limited quantity; moreover, no total synthesis of hypocretenolides had been reported, impeding structure–activity relationship (SAR) studies and the development of potential derivatives.

To circumvent this limitation, Chen *et al.*[211] in 2024 devised an efficient approach for the first collective total synthesis of four hypocretenolides, involving the Corey–Chaykovsky reaction as a key step to introduce the cyclopropane moiety. The synthesis was initiated with the economical feedstock (*S*)-carvone **146**, which underwent the Corey–Chaykovsky reaction with Me_3SOI and sodium hydride in DMSO at 50 °C to afford cyclopropane ring **147** in 96% yield. The cyclopropane-endowed compound **147** was treated over a number of steps to afford the allylic chlorinated product **148**. The alkene lithium obtained from compound **149** mounted a nucleophilic attack on compound **148**, followed by TBAI-induced alkylation and desilylation to afford an alcohol **150** in 30% yield. Then, DMP oxidation of **150** gave aldehyde in 80% yield, followed by oxime intermediate formation with $NH_2OH{\cdot}HCl$. The intermediate was subjected to intramolecular 1,3-dipolar cycloaddition, which gave the isoxazoline product **151** in 75% yield with the desired 5/6/7 ring system. In the next step, the isoxazoline ring was subjected to Fe/AcOH reduction, which gave the desired dienone **152** in 87% yield. The dienone **152** was treated over several steps to furnish hypocretenolide **153** (Scheme 21).

Damascenolide™ [4-(4-methylpent-3-en-1-yl)furan-2(5*H*)-one] is isolated from *Rosa damascena* (damask rose),[212] with a characteristic citrus-like odor that imparts blooming and natural aroma character to artificial rose. Miyazawa *et al.* explored the SOR (structure–odor relationships) of a total of 24 analogs of damascenolide™ and studied their syntheses for developing more aroma compounds.[213,214] Their previous research on the analogs of damascenolide™ revealed that slight structural changes significantly influenced the odor.

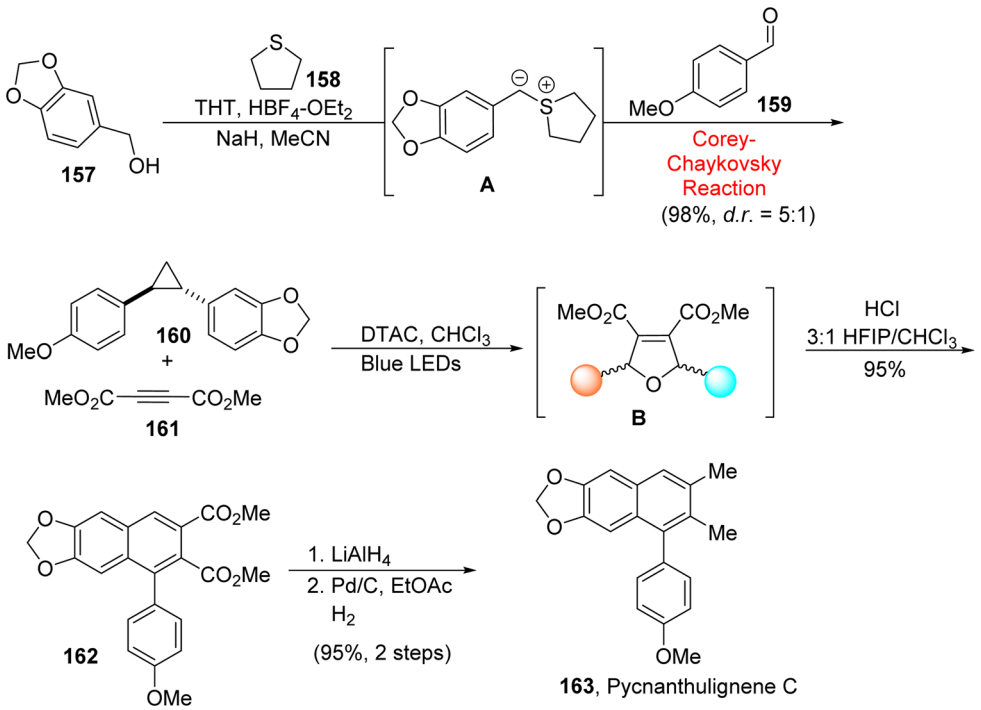
In 2021, Miyazawa *et al.*[215] synthesized 10 analogs of damascenolide™ and performed odor evaluation; the analogs were divided into 3 groups (dimethylated, cyclopropanated and other analogs). Group 2, featuring cyclopropanated analogs, was selected because previous evaluation showed that cyclopropanation alters the odor of various odor-active compounds. Initially, Miyazawa *et al.* attempted to synthesize cyclopropanate damascenolide™ but failed. However, the Corey–Chaykovsky cyclopropanation was successfully used to synthesize cyclopropane **156**. The synthetic intermediate of damascenolide™ **154** was subjected to the Corey–Chaykovsky reaction using trimethylsulfoxonium iodide and KO*t*Bu in DMSO at room temperature to yield compound **155**. The EE group of compound **155** was removed using aqueous HCl in THF, followed by one-pot lactonization to afford compound **156** in 18% yield (2 steps) (Scheme 22).

3 Miscellaneous

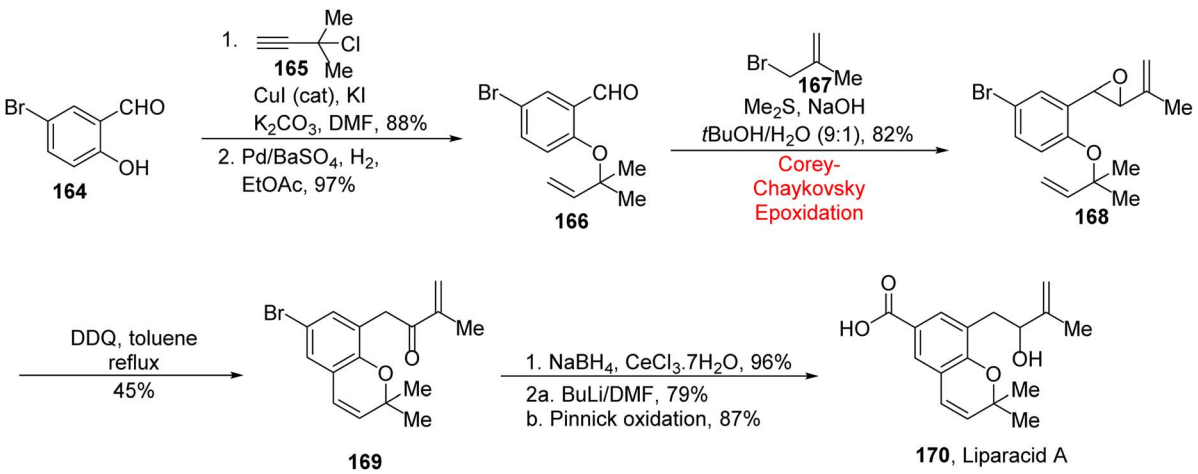
Classical lignans, specifically caryltetralin, arylnaphthalene and dihydronaphthalene, are bioactive natural products.[216] The utilization of their synthetic derivatives as pharmaceutical agents prompted research efforts into their synthetic strategies. The variety of existing methods for preparing natural complexes often fall short in interrogating the SAR (structure–activity relationship). Therefore, modern techniques emphasize diversity and modularity. Alfonzo and co-workers reported a unified method that utilized THFs (tetrahydrofurans) as key scaffolds to synthesize various CLs and their subtypes.[217]

In 2020, Alfonzo *et al.*[218] reported that a modular one-pot method enabling the efficacious synthesis of arylnaphthalene and dihydronaphthalene natural products can be carried out with simply accessible precursors (epoxides and dipolarophiles) covering multiple oxidation states, *e.g.*, pycnanthulignene C. These are also known to exhibit anti-microbial action against a range of drug-resistant microbes.[219] The total synthesis of pycnanthulignene C **162** involved the Corey–Chaykovsky reaction and photoredox-catalyzed [3 + 2] cycloaddition as key steps. Firstly, sulfonium ylide **A** was prepared by treating the benzyl alcohol **157** with tetrahydrothiophene **158** and $HBF_4{\cdot}OEt_2$, then with NaH in the MeCN solvent at 0–23 °C. The ylide **A** was subjected to a one-pot Corey–Chaykovsky reaction with aldehyde **159** to afford epoxide **160** in 98% yield (d.r. = 5 : 1). Following this, the epoxide mixture in $CHCl_3$ (chloroform) employing DTAC underwent [3 + 2] cycloaddition, after which the addition of HFIP and HCl at 10 °C without changing the solvent furnished the dihydronaphthalene **162** in 95% yield (r.r. > 20 : 1). Finally, the reduction *via* $LiAlH_4$ and the hydrogenation of **162** in EtOAc (ethyl acetate) afforded pycnanthulignene C **163** in 88% overall yield, over four steps (Scheme 23).

Liparacid A **170**,[220] a rare natural product, was isolated from the rhizoma of *Liparis nakaharai* in 2007, and it has relevance in Chinese folk medicine as an anti-tumor agent. In 2020, Song *et al.* reported the first total synthesis of liparacid A **170**, featuring CuI-catalyzed etherification and Corey–Chaykovsky epoxidation as key reactions.[221] The synthetic route commenced



Scheme 23 Synthesis of pycnanthulignene C **162**.



Scheme 24 Synthesis of liparacid A **170**.

with the CuI-catalyzed etherification[222] of 4-bromosalicylaldehyde **164** to furnish a product in 88% yield, and a subsequent Lindlar reduction[223] gave compound **166** in 97% yield. Following this, compound **166** was subjected to the Corey–Chaykovsky reaction[224] employing dimethyl sulfide and NaOH in *t*BuOH/H_2O (9 : 1) solvent to synthesize epoxide **168** (2 steps) in 80% yield. In the next step, the new cascade technique was applied to epoxide **168**, which resulted in the ketone **169** with the desired 2*H*-chromene framework in 45% yield. Ultimately, the three-step sequence, including the Luche reduction[225] of ketone **169** (96% yield), formylation (79% yield), and Kraus–Pinnick oxidation (87% yield), produced the liparacid A **170** in 87% yield (Scheme 24).

4 Conclusion

To summarize, this review presents a detailed overview of the applications of the Corey–Chaykovsky reaction in the total syntheses of various natural products and their analogs. The Corey–Chaykovsky reaction provides an efficient stereoselective route to access cyclopropanes as well as other heterocycles, such as epoxides and aziridines, in high yields under mild conditions. In recent years, this reaction has been consistently proven as a key transformational tool in the toolkit of synthetic organic chemistry, particularly for the synthesis of complex natural products. This review underscores the synthetic utility and stereoselectivity of CC methodology in the synthesis of a diverse

range of natural products, including alkaloids, terpenoids, depsipeptides, polyketides and amino acids. We anticipate that the continued methodological advances in CCR will consolidate it as a reliable and robust technique towards the total synthesis of natural products.

Conflicts of interest

The authors declare no conflicts of interest.

Data availability

No primary research results, software or code has been included and no new data were generated or analysed as part of this review.

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